

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 02 March 2001 (02.03.01)	
International application No. PCT/US00/05194	Applicant's or agent's file reference 7584L/VB
International filing date (day/month/year) 01 March 2000 (01.03.00)	Priority date (day/month/year) 01 June 1999 (01.06.99)
Applicant YOUNGQUIST, Robert, Scott et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

21 December 2000 (21.12.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer R. Forax Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY**PCT****INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 92271/9010	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/05194	International filing date (day/month/year) 01/03/2000	Priority date (day/month/year) 01/06/1999
International Patent Classification (IPC) or national classification and IPC C07D295/08		
Applicant THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTRE		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application</p>		

Date of submission of the demand 21/12/2000	Date of completion of this report 08.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Scruton-Evans, I Telephone No. +49 89 2399 8272



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/05194

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-51 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages: _____
- the claims, Nos.: _____
- the drawings, sheets: _____

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.

claims Nos. 1-10(PARTLY).

because:

the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. 1-10(PARTLY).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the standard.

the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2,4,6,10
	No:	Claims 1,3,5,7-9
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-10

Industrial applicability (IA) Yes: Claims 1-9

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No: Claims

2. Citations and explanations
see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

- D1: EP-A-0580550
- D2: Journal Of Medicinal Chemistry,us,american Chemical Society.
Washington (01-01-1995), 38, 695-707
- D3: WO-A-9625943
- D4: GB-A-2138286
- D5: US-A-5284971
- D6: US-A-5061798

As indicated in the Search Report, only a partial search was carried out, and thus this opinion is limited to that subject matter which has been searched.

With regard to the requirement for novelty (Article 33(2) of the PCT), the compounds of the present application differ from those of D1,D2 and D5 in that they all disclose biaryl ether compounds, and with those of D3 and D4 in that they do not specifically disclose biaryl compounds. Document D6 discloses certain compounds which have been partly disclaimed from the present application (see definitions of R₄,) but as Ar in D4 is not only aryl, the disclaimer should also exclude those wherein R₄ is heteroarylalkyl, as the

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EXAMINATION REPORT - SEPARATE SHEET**

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specificity of D4 is greater than that of the present application when referring to the definition of the group Ar in D4. Article 33(2) is thus not satisfied re D4 for claims 1,3,5 and 7-9.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the following comments are made.

The compounds of the present application are described as being useful for treating hair loss, their action being thought to be due to interaction with hair-selective thyroid hormone receptors. It is known from D4 and D3 in general, that hair growth can be promoted using thyroid hormones. The compounds of D1,D5,D6 and D2 are known thyromimetic compounds, and these overlap with (in the case of D6) or differ from those of the present application essentially in the nature of the biaryl-coupling (O,S or SO₂). The compounds disclosed in D2 and D6 are said to have no adverse cardiac effects. The man skilled in the art, faced with the problem of providing further novel compounds to promote hair growth, and knowing that thyroid hormones are useful in the treatment of hair loss, would have prepared the compounds of the present application differing as they do only in the nature of the CR₆R₆' re those of the prior art (CH₂ is known to be equivalent to O and S from D6), expecting them to have a thyromimetic activity without adverse cardiac effects, and thus to be useful in the treatment of hair loss. Thus the problem to be solved must be seen as the provision of further novel compounds with unexpected advantages re the prior art. In the absence of such evidence, Article 33(3) of the PCT cannot be considered to have been satisfied. Such evidence could take the form of, for example, comparative data between a compound from D6 and one from the present application differing only in the nature of the R₄ group. Only those compounds which provide a solution to the problem should be claimed, and the terms such as "biohydrolyzable amides, esters and imides thereof" and "aryl","heteroaryl","alkyl" without C-atom content etc are all such that the scope of the claim extends way beyond those compounds actually prepared and a reasonable generalisation thereof. Furthermore, it would appear from the description, page 4 ff that the term "alkyl" for example is intended to include substituted moieties, which are not defined, nor is this clear from the claims.

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International application No. PCT/US00/05194

For the assessment of the present claim 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL SEARCH REPORT

Int'l. application No
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/08 C07C233/25 C07C233/29 A61K31/165 A61P17/14
A61K31/535 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 580 550 A (CIBA GEIGY AG) 26 January 1994 (1994-01-26) the whole document ---	1-10
A	N YOKOYAMA: "Synthesis and structure-activity relationships of oxamic acid and acetic acid derivatives related to L-thyronine" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 38, 1 January 1995 (1995-01-01), pages 695-707, XP002080908 ISSN: 0022-2623 the whole document --- --/-	1-10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 July 2000

Date of mailing of the international search report

12.07.00

Name and mailing address of the ISA

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Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 25943 A (LIFE MEDICAL SCIENCES INC) 29 August 1996 (1996-08-29) cited in the application the whole document ----	1-10
A	GB 2 138 286 A (MORTIMER DR CHRISTOPHER HARRY) 24 October 1984 (1984-10-24) cited in the application the whole document ----	1-10
Y	US 5 284 971 A (WALKER KEITH A ET AL) 8 February 1994 (1994-02-08) cited in the application the whole document ----	1-10
X	US 5 061 798 A (EMMETT JOHN COLIN ET AL) 29 October 1991 (1991-10-29)	1,3,5, 7-9
Y	see especially definitions of Ar -----	1-10

INTERNATIONAL SEARCH REPORTInt'l Application No.
PCT/S 00/05194**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: **1-10 partly**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00/05194

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10 partly

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject matter for which protection might be legitimately sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to all of the compounds of Table 1 and the examples, and a generalisation thereover such that R3 is as in claim 1, R is isopropyl or t-butyl, R₂,R₁ and R₅ are H, R₆ and R_{6'} are H, OH or together =O, R₁₀ and R₇ are H and R₉ and R₈ are CH₃ or Cl, with Y as a bond and X as NZ or NH.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l application No
PCT/US 90/05194

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0580550	A	26-01-1994	AT 159515 T AU 4208193 A CA 2100817 A DE 69314718 D DE 69314718 T DK 580550 T ES 2108855 T FI 933260 A GR 3025517 T HU 64512 A,B JP 6172275 A NO 932614 A NZ 248181 A US 5401772 A US 5569674 A US 5654468 A ZA 9305196 A	15-11-1997 27-01-1994 22-01-1994 27-11-1997 26-02-1998 02-02-1998 01-01-1998 22-01-1994 27-02-1998 28-01-1994 21-06-1994 24-01-1994 27-11-1995 28-03-1995 29-10-1996 05-08-1997 07-07-1994
WO 9625943	A	29-08-1996	AU 4990496 A CA 2213481 A EP 0812210 A JP 9010915 A	11-09-1996 29-08-1996 17-12-1997 14-01-1997
GB 2138286	A	24-10-1984	AT 29382 T AU 566833 B AU 2828484 A CA 1226524 A DE 3465879 D DK 607284 A EP 0123528 A WO 8404038 A GR 81975 A JP 60501057 T NO 845096 A NZ 207923 A PT 78456 A ZA 8402986 A	15-09-1987 29-10-1987 07-11-1984 08-09-1987 15-10-1987 18-12-1984 31-10-1984 25-10-1984 12-12-1984 11-07-1985 18-12-1984 28-07-1988 01-05-1984 26-06-1985
US 5284971	A	08-02-1994	NONE	
US 5061798	A	29-10-1991	AT 61581 T AU 577917 B AU 5221986 A CA 1319148 A CN 1010310 B DE 3678000 D DK 18586 A,B EP 0188351 A ES 551005 D ES 8800157 A FI 860229 A GR 860122 A HU 40401 A,B IE 58867 B IL 77605 A JP 7103070 B JP 61167643 A KR 9311302 B	15-03-1991 06-10-1988 24-07-1986 15-06-1993 07-11-1990 18-04-1991 19-07-1986 23-07-1986 01-11-1987 01-01-1988 19-07-1986 19-05-1986 28-12-1986 17-11-1993 09-02-1990 08-11-1995 29-07-1986 29-11-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US 00/05194

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5061798 A		NO 860159 A	21-07-1986
		NZ 214843 A	24-02-1989
		PH 22691 A	14-11-1988
		PT 81844 A,B	01-02-1986
		US 4826876 A	02-05-1989
		US 4910305 A	20-03-1990
		US 4766121 A	23-08-1988
		ZA 8600319 A	27-08-1986
		ZW 886 A	13-05-1987